Basic Research · Proteomics · Computational Biology · Bioengineering · Mouse Genetics · Functional Genomics · Chemical Genomics · Drug Discovery

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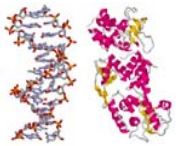
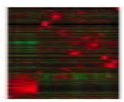
Target ID and Drug Discovery: The 35,000 Foot View

Target Identification & Validation

Target Identification → In vitro validation → In vivo

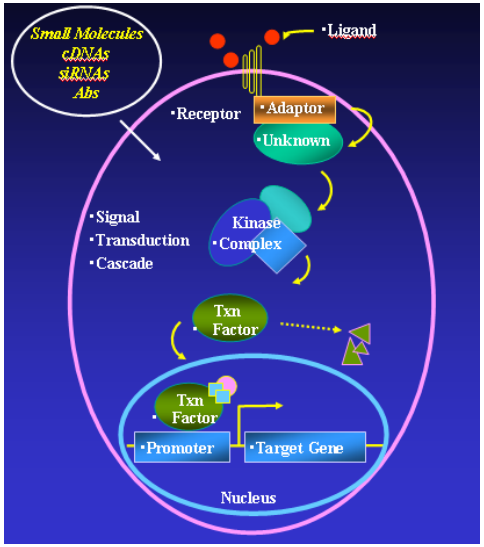
Bioinformatics	RNA Dynamics	Cell-Based Screening	Mouse Genetics
			
Sequence	**Expression**	**cDNA Overexpression** **siDNA/RNA Knockdown** **Small Molecules**	***In vivo*** **Validation**

Drug Discovery Pipeline

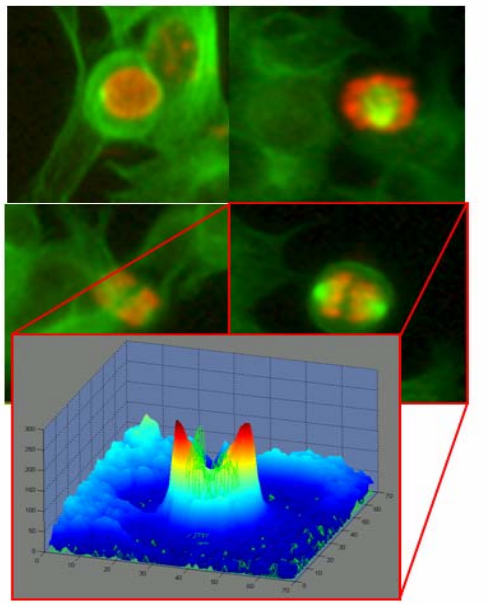
Target Selection → Target Validation → Target Screening → Medicinal Chemistry → Pre-Clinical Studies → Clinical Trials

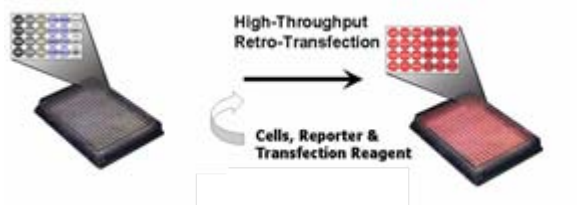
- Target Selection, Target Validation → Target Identification
- Target Screening → Hit prioritization
- Medicinal Chemistry → Lead Optimization

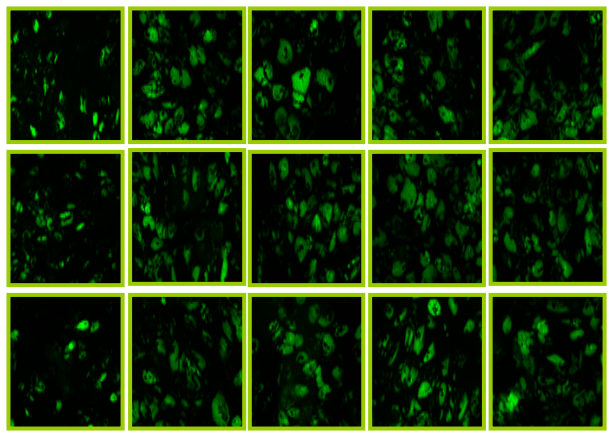
Cellular Genetics Screening Automation



- Automated screening of cDNA/siRNA/shRNA collections (>150,000 wells/run)
- High-throughput Automated Lentiviral Packaging
- Automated hitpicking of screen hits by gene family
- High-throughput image- and FACS-based screens
- In-house data tracking LIMS system (Camaro)
- 150+ unbiased functional genomic screens



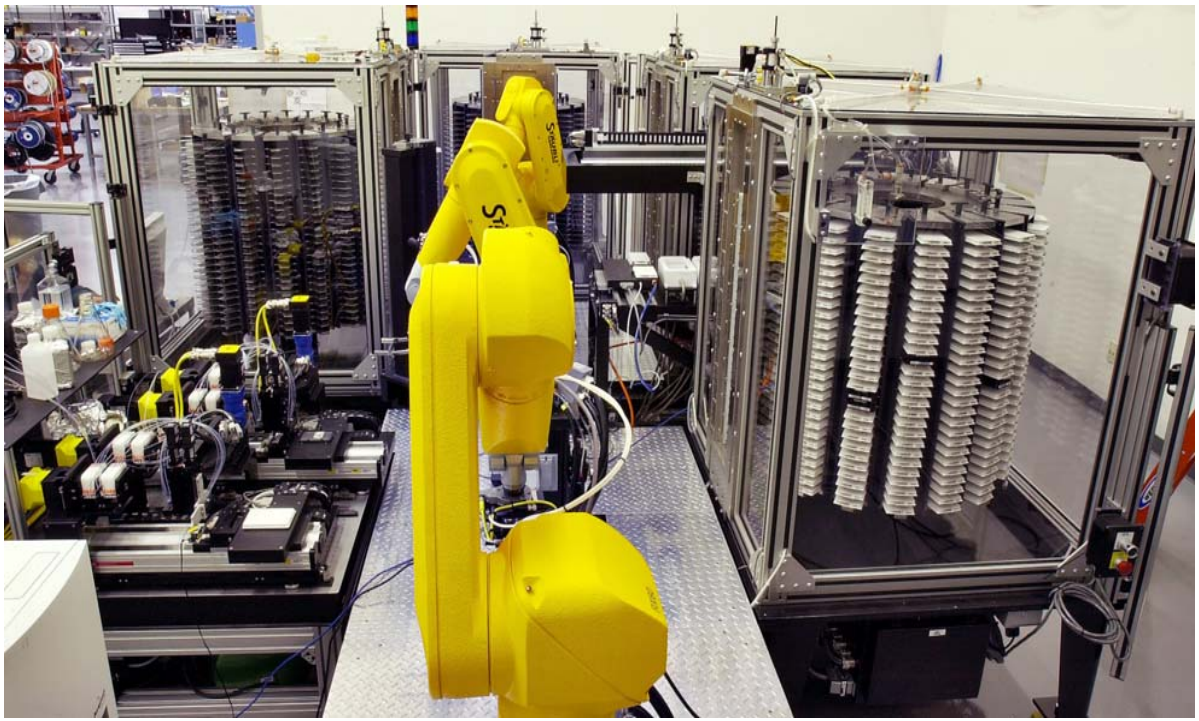




controls Enhancers of Adipocyte Differentiation

GNF

Small Molecule Screening Automation

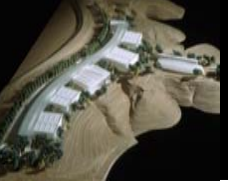


Distinguishing features

- 1,800,000 compounds (up to 2.0M)
- 1.5 cents/well (1/20th of conventional)
- $15,000/assay
- 5, 50 or 500 nl compound/well
- cellular reporter and biochemical screens

80+ screens/year
1,000,000+ comp.s/day
(188 screens to date)

Screening has become a low cost, high throughput, robust tool



Major Challenges and Possibilities for ESC High-Throughput Cell-based Screening

(a GNF perspective)

[1] Costs

Possible solutions: Centralized “California” core facility (i.e. NIH Roadmap), miniaturization of assays

[2] Technical Roadblocks : High-throughput Manipulation of hESCs, Assay Detection, etc.

Possible solutions: Development of clonal cell lines suited to HTS, Chemical definition of culture conditions, ESC technology transfer to screening centers, Support for assay development

[3] Cultural Roadblocks: Translational Research Between Academic and Biotech Sectors

Possible solutions: Sponsorship of joint Academic-Industrial Initiatives

[4] Target Deconvolution (Small Molecule Screening)

Possible solutions: Promote Genetic and Target Identification Projects

[5] Validation of Results from Cellular Assays

Possible solutions: Encourage the development of *in vivo* models and transplantation methodologies for validation studies

[6] Exploratory Chemistry

Possible solutions: Provide medicinal chemistry support (i.e. SAR studies) for hESC projects

[7] Large-scale (GMP) Production

Possible solutions: Build upon SOP for biologics manufacturing. Automation, standardization, non-invasive QC (i.e. image analysis)